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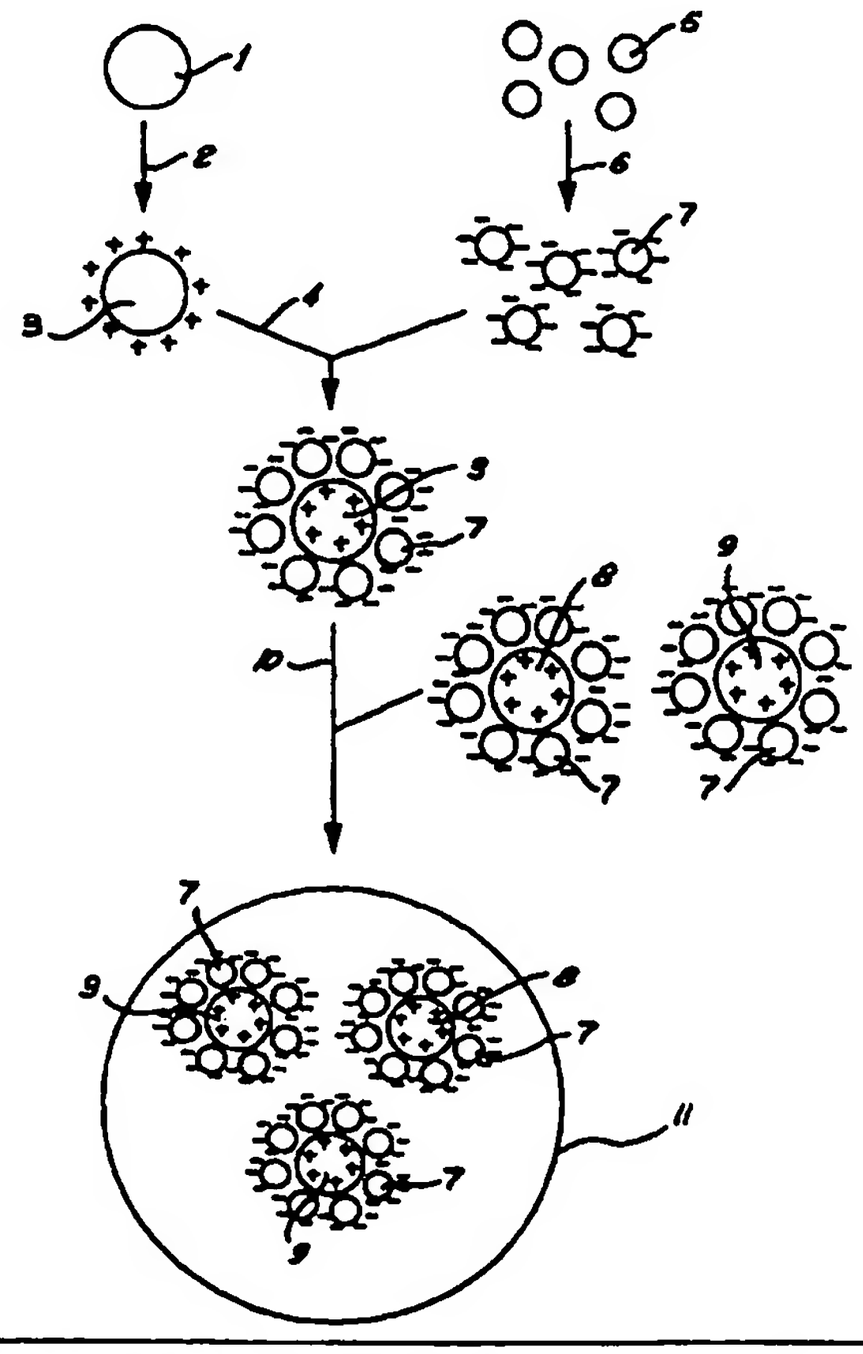
(54) Title: IMPROVED COMBINATION DOSE UNIT

(57) Abstract

This invention relates to a combination therapy dose unit and a method of preparing such a dose unit. The method of preparation is designed to prevent interaction between a plurality of active agents in a combination therapy dose unit, and comprises the steps of charging particles of an active agent, charging particles of an inert particulate medium with a charge of opposite polarity to that of the charged particles of the active agent and allowing the charged inert particulate medium particles to electrostatically adhere to the charged particles of the active agent, thereby to coat the active agent with inert particulate medium. Thereafter other active agents can be treated in a similar manner and the electrostatically coated active agents can be combined, and may include other non-coated active agents, into a single combination therapy dose unit such as a tablet.



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TITLE: "IMPROVED COMBINATION DOSE UNIT"

TECHNICAL FIELD

This invention relates to an improved combination medication, a process of manufacturing such a medication and therapeutic methods using such a medication.

Although the invention will be described with reference to a medication for treating gastrointestinal disorders associated with *Helicobacter pylori*, it is to be understood that it may be adapted to other forms of combined medication or therapy. Such variations will be within the knowledge of those skilled in the art and the scope of the invention.

BACKGROUND ART

"Triple Therapy" is a multiple-part therapy for gastrointestinal or stomach ulcers resulting from infection by *H. pylori*. The method involves the administration of tablets or capsules of a bismuth compound and two types of antibiotics for eg. 12 days. In a five-times per day regimen, a patient ingests 15 tablets or capsules, making it a tedious and complicated protocol and may reduce compliance and hence efficacy of treatment.

The recommended dosage of each active component in "Triple Therapy" is:

- bismuth subcitrate (108 mg) or bismuth subsalicylate (260 mg);
- tetracycline HCl (250 mg) or amoxycillin (500 mg) and metronidazole (250 mg).

It has hitherto not been possible to combine all three of the active agents into a single dose unit such as a tablet or capsule.

One problem is that the mass of a single capsule or tablet which contains the three agents will, in the absence of necessary excipients or auxiliaries, already be great and far exceed the maximal mass of components allowed for the production of a reasonably sized tablet/capsule. In addition such a mass cannot be expected to be ingested or swallowed by most patients without difficulty.

A second problem relates to cross-reactions and degradation. In a single unit containing the three agents in the presence of water of hydration and residual oxygen, ongoing oxidation will result in the degradation and/or inactivation of the active components and concomitantly lead to production of undesirable, toxic by-products. For instance, bismuth subsalicylate may oxidise to form a product which escapes from the bowel into the brain and ultimately cause encephalopathy. Tetracycline HCl degrades with time to form unwanted 4-epi-tetracycline and a side product which is toxic to the kidneys. The cross-reactivity between the agents also create a further problem by increasing the levels of undesirable by-products. Thus, if a single unit were to be stored in a warehouse or on a pharmacist's shelf, the risk of obtaining a therapeutically inactive but toxic composition is high.

It has been suggested that the three agents may each be micro-encapsulated as separate microspheres which are then incorporated into a single capsule. However, the high dosage of each component and the large volume of "empty space" between the thickly coated microcapsules render the production of a capsule that is easily swallowed and within the bounds of manufacturing standards impractical. The minimum effective dose of the combined agents is more than 600 mg and far exceeds the maximum practical mass for a capsule, even if it is elongated.

Furthermore, orally ingested bismuth compounds stain the oral mucosa a brown colour. It is therefore desirable to obtain a product which does not dissolve in the mouth but which is capable of dissolving rapidly within the stomach.

The present invention ameliorates one or more of the disadvantages described above.

SUMMARY OF THE INVENTION

In a first aspect, the invention consists in a method of preventing interaction between a plurality of active agents at risk of interacting in a combination therapy dose unit, said method comprising the steps of:

(i) charging particles of a first active agent,

(ii) charging particles of an inert particulate medium with a charge of opposite polarity to that of the charged particles of the first active agent,

(iii) allowing the charged inert particulate medium particles to electrostatically adhere to the charged particles of the first active agent thereby to coat the active agent with inert particulate medium; and

(iv) combining the coated first active agent particles with other active agents of the dose unit.

In the second aspect, the invention consists in a combination therapy dose unit comprising at least one active agent which has been coated with an inert particulate medium according to the method described above.

A third aspect of the invention relates to a method of preventing or treating a disorder in a host requiring administration of a plurality of active agents comprising the administration of a combination therapy dose unit as described above.

In a preferred embodiment the medium which is in electrostatic communication with an active agent includes magnesium stearate, silicon dioxide or other inert or lubricating material. Such a medium is preferably electrically charged by using the principles of static electricity. For instance, the medium may be passed over a negative electrode at extra high tension ("EHT") or high voltage and very low current to render the medium negatively charged.

In another preferred aspect, the invention provides a dose unit as described above, in combination with a micro-encapsulated proton pump inhibitor.

The invention will now be described by way of example to illustrate preferred embodiments only and is not intended to limit the scope in any way.

BRIEF DESCRIPTION OF THE FIGURE

Figure 1 shows a preferred process of making a combination therapy dose unit.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

In Figure 1, a microparticle of a first active agent 1, such as bismuth subsalicylate, and containing a polyvinylpyrrolidone binder, a lactose filler and an exploder, is prepared by a known process of granulation. It is then passed 2 over a positive electrode in a closed vessel at EHT (20,000-30,000 V) and very low current (50-120 milliamps) at 1.5-2.0 litres per minute to remove the electrons and render the surface of the microparticle positively charged 3.

To the "primed" microparticle 3 is then added 4 micronised and microfine grade inert particulate medium 5, such as magnesium stearate, which has been rendered negatively charged by passing 6 over a negative electrode in a closed vessel at EHT (20,000-30,000 V), very low current (50-120 milliamps) and 1.5-2.0 litres per minute. The negatively charged inert particulate medium 7 is allowed to form a microscopic coat 5 around the positively charged particle of the first active agent.

Microparticles of a second active agent 8 such as tetracyline, and of a third active agent 9, for example metronidazole, are each prepared in the same manner using the same or different inert particulate medium and the three coated, active agents are ultimately mixed together 10 in the required proportions, for example 100 mg bismuth, 200 mg tetracycline HCl and 200 mg metronidazole. The molecular layer or coat of the inert particulate medium insulates the active agents from each other and so prevents them from cross-reacting and forming toxic or unwanted by-products. The mixed microparticles are blended with binders, fillers and disintegrants/exploders as above and the whole mixture can be then compressed into a tablet 11 which contains the correct dosage of each active agent in a honeycombed or web-like matrix represented in part in Figure 1 by three microparticulate cells of, for example, coated bismuth subsalicyclate 3, tetracycline 8 and metronidazole 9, respectively.

The microparticles which are to be electrostatically coated are preferably milled and sieved to a granular mass of uniform particle size which, according to the compound used, may range from 10-150 μm. It is also preferable that the microparticles or microgranules are subjected to complete drying in a fluid bed dryer and to intense high energy movement or flow in the dryer both before and after milling and sieving. This enhances the acceptance of an electrical charge in the priming

process that follows as the high energy and dry, hot friction will render the microparticles more adaptable to the electrical change.

The inert particulate medium for electrostatically coating the active components is desirably any inert material that acts both as a lubricant and a protective agent eg. one or more of magnesium stearate or silicon dioxide or the like. A micronised and microfine grade medium is preferred.

Auxiliaries such as binders, fillers or disintegrant/exploder which may be included are preferably selected from polyvinyl pyrrolidone, microcrystalline cellulose, lactose granules, Crospovidone XL, Explotab (sodium starch glycolate) or Croscarmellose sodium (sodium cellulose glycolate) or the like.

Each individual active component can vary from 2 to 500 mg. Bismuth compounds suitable in the present invention include those selected from the group consisting of bismuth aluminate, bismuth subcarbonate, bismuth subcitrate, bismuth citrate, tripotassium dicitrato bismuthate, bismuth subgallate, bismuth subnitrate, bismuth tartrate, bismuth salicylate, bismuth subsalicylate, and mixtures thereof are preferred bismuth salts for use in this invention. A variety of bismuth containing compositions are available commercially including, for example, DeNol, containing tripotassium dicitrato bismuthate (sold by Gist-Brocades N.V.), Noralac, containing bismuth aluminate, alginic acid, and magnesium carbonate (manufactured by North American Pharmaceuticals), Roter bismuth, containing bismuth subnitrate (sold by Roter Laboratories), Fensobar Polvo, containing bismuth subcarbonate among other materials (manufactured by USV Pharmaceutical Corporation), and Pepto-Bismol, containing bismuth subsalicylate (sold by The Procter & Gamble Company). The lower dosage of bismuth contemplated by the invention may range from 20-200 mg per tablet, preferably 100 mg.

Preferably, the antibiotic or antibacterial agent may be selected from one or more of tetracyclines, penicillins, quinolones, cephalosporins, furazolidones, lincosamides, nitrofurantoins, nitromidazoles, macrolides and/or polypeptides.

Preferably, the second antibiotic or antibacterial agent is selected from one or more of quinolones, furazolidones, nitrofurantoins, and/or metronidazoles.

More preferably the first antibiotic or antibacterial agent is selected from tetracyclines and/or penicillins and the second antibiotic or antibacterial agent is a metronidazole. The first and second antibiotics or antibacterial agents are not the same, although they may be selected from the same class.

The tetracyclines include tetracycline, oxytetracycline, doxycycline, demeclocycline, methacycline and minocycline.

The penicillins include penicillin G, penicillin V, oxacillin, nafcillin, ampicillin, amoxicillin, cloxacillin and carbenicillin.

The nitronidazoles include metronidazole and tinidazole.

Rifanpin, trimethoprim and/or nalidixic acid may also be used.

The cephalosporins include cephalexin, cefaclor, cephapirin, cephradine and cefadroxil as well as second and third generation cephalosporins.

The polypeptide antibiotics include plolymixin B, bacitracin, colisin sulfate and/or spectinomycin HC1.

The macrolides include erythromycin, clarithromycin, azithromycin, and roxithromycin.

Quinolones include ciprofloxacin, norfloxacin and ofloxacin.

Lincosamides include lincomycin and clindamycin.

Preferably a combination of antibiotics is employed. For example the dosage range of the antibiotics may be 20-300 mg eg. 20-250 mg per capsule/tablet tetracycline HCl and 50-300 mg of metronidazole.

When tetracycline HCl is used eg. in a tablet, it may be desirable to also incorporate a small amount of EDTA and/or vitamin E powder (d-alphatocopherol acid succinate). The preferred range of EDTA is 0.01-0.05% by weight of the tablet whilst that of vitamin E is 0.01%-2.0% by weight of the tablet EDTA is a chelating agent which scours stray metal ions to form insoluble, inert and innocuous complexes and further prevents undesirable degradation of the active components. The addition of vitamin E also helps to prevent oxidation.

Preferably the treatment is combined with the administration of an acid suppressant such as a histamine$_2$ antagonist such as cimetidine, ranitidine or famotidine to effect symptomatic relief and ulcer epithelialization. Other acid suppressants may

be used instead of a histamine $_2$ antagonist such as benzimidazole or prostaglandins. Alternatively, the histamine $_2$ blocker, proton pump inhibitor or other acid suppressant can be combined with the pharmaceutical composition of the present invention.

In a preferred aspect of the invention, the dose unit may additionally comprise a microencapsulated proton-pump inhibitor such as omeprazole, lansoprazole, pantoprazole or the like. The dosage may be 2-40 mg, preferably 10 mg per tablet. The microencapsulation prevents cross-reaction between the inhibitor and the three active agents. The proton pump inhibitor potentiates eradication of *H. pylori* by acid reduction, antibiotic activation and direct inhibition of proton pumps in the bacteria.

During the manufacture of the dose unit, it is preferable that exposure of all the components to oxygen is kept to a minimum. This can be achieved by tabletting and mixing the components under a blanket of nitrogen. The resulting dose unit can be further protected from oxygen, humidity, heat and hence degradation and/or inactivation by being individually packaged in blister packs, preferably in a nitrogen gas atmosphere, thus creating a negative oxygen gradient outside each tablet.

The active components which may be combined in dose units in accordance with the invention are preferably selected from the group comprising: a) bismuth, tetracycline and metronidazole, b) bismuth, amoxycillin, metronidazole or tinidazole, c) bismuth, tetracycline and azithromycin, d) a macrolide, proton pump inhibitor and a nitromidazole such as:

i) clarithromycin, omeprazole and tinidazole or

ii) clarithromycin, omeprazole and metronidazole.

Dose units in accordance with the invention may contain two or more of the active agents herein described or two or more agents for treating other diseases. It is also possible to co-administer the dose units with separate, known units or capsules containing other drugs eg. proton pump inhibitors. The dose units may be administered once daily through to five times daily and can be taken between two and twenty-eight days. The invention may be embodied in various other forms in a manner known and understood by those skilled in the art.

The invention, by enabling normally cross-reactive components of a therapeutic regimen to be combined safely into a single unit provides clinically acceptable, stable and efficacious medication.

The combination of the three components of "Triple Therapy" in a single unit allows not only for the delivery of a considerably lower dose and bulk volume but has also maintained eradication of about 90% of *H. pylori*.

The unique, electrostatic bonding of inert medium to each drug provides a microscopic layer of skin or coat which contributes minimally to the "dead" or "empty" spaces between each drug when mixed into a dose unit such as a tablet. This allows a unit of smaller and desirable size to be produced and also enables the active components to be uniformly combined with virtually no interaction or cross-reaction. Upon ingestion of the tablet, the intercellular exploders ensure the prompt disintegration of the tablet and dispersion of the encapsulated and insulated active agents. The intracellular exploders blended with each agent then ensures its dispersion from the micronised, insulating coat.

The combination therapy dose units contemplated herein may be used for the treatment of *Helicobacter* infection in animals as well as man. The infections may be related to various disease states associated with *H. pylori* eg. gastroduodenal ulcers, non-ulcer dyspepsia, reflux symptoms, mucosa associated lymphoid tissue lympohoma (MALT-lymphoma), gastric mucosal atrophy, intestinal metaplasia, dysplasia, carcinoma, reflux oesophagitis and gastritis. Asymptomatic carriers of the infection may also be treated with the dose unit.

Although the present invention has been described in terms of preferred embodiments it will be evident to those skilled in the art that variations and modifications are possible whilst not departing from the basic principles and the spirit of this invention.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method of preventing interaction between a plurality of active agents at risk of interacting in a combination therapy dose unit, said method comprising the steps of:

(i) charging particles of a first active agent,

(ii) charging particles of an inert particulate medium with a charge of opposite polarity to that of the charged particles of the first active agent,

(iii) allowing the charged inert particulate medium particles to electrostatically adhere to the charged particles of the first active agent thereby to coat the active agent with inert particulate medium; and

(iv) combining the coated first active agent particles with other active agents of the dose unit.

2. A method according to claim 1, further comprising the steps of:

(i) charging particles of a second active agent,

(ii) charging particles of the same or a different inert medium with a charge of opposite polarity to that of the charged particles of the second active agent,

(iii) allowing the charged inert particulate medium particles to electrostatically adhere to the charged particles of the second active agent; and

(iv) combining the coated second active agent with the coated first active agent.

3. A method according to any one of the preceding claims, wherein the active agents are a bismuth compound and at least an antibiotic or antibacterial substance.

4. A method according to claim 3, wherein the bismuth compound is selected from bismuth aluminate, bismuth subcarbonate, bismuth subcitrate, colloidal bismuth subcitrate, bismuth citrate, tripotasium dicitrato bismuthate, bismuth subgallate, bismuth subnitrate, bismuth tartrate, bismuth salicylate, bismuth subsalicylate or combinations thereof.

5. A method according to any one of the preceding claims, wherein the antibiotic or antibacterial agent is selected from one or more of tetracyclines, penicillins, quinolones, cephalosporins, furazolidones, lincosamides, nitrofurantoins, nitromidazoles, macrolides and/or polypeptides.

6. A method according to claim 5, wherein the antibiotic is tetracycline, metronidazole or a combination thereof.

7. A method according to any one of the preceding claims, wherein the combination therapy dose unit further comprises an acid suppressant.

8. A method of claim 8, wherein the acid suppressant is electrostatically bonded to an inert particulate medium according to the method of claim 1.

9. A method of claim 7 or claim 8, wherein the acid suppressant is a histamine antagonist.

10. A method according to claim 9, wherein the histamine antagonist is selected from cimetidine, ranitidine, famotidine, nazatidine or prostaglandins.

11. A method according to claim 7 or claim 8, wherein the acid suppressant is a proton pump inhibitor.

12. A method according to claim 11, wherein the proton pump inhibitor is selected from omeprazole, lansoprazole or pantoprazole

13. A method according to any one of the preceding claims, wherein the inert particulate medium is magnesium stearate or silicon dioxide.

14. A method according to any one of the preceding claims, wherein the coating of the active agent with inert particulate medium is performed under a blanket of nitrogen.

15. A method of any one of the preceding claims further comprising the step of combining the particles of at least one active agent coated with the inert particulate medium into a tablet.

16. A combination therapy dose unit comprising at least one active agent which has been coated with an inert particulate medium according to the method of claim 1.

17. A combination therapy dose unit according to claim 16, further comprising a proton pump inhibitor.

18. A combination therapy dose unit according to claim 16 or claim 17, wherein the dose unit comprises one of the following combinations:

a) bismuth, tetracycline and metronidaziole;

b) bismuth, amoxycillin, metronidazole or tinidazole;

c) bismuth, tetracycline and azithromycin; or

d) a macrolide, proton pump inhibitor and a nitromidazole combination consisting of:

i) clarithromycin, omeprazole and tinidazole or

ii) clarithromycin, omeprazole and metronidazole.

19. A combination therapy dose unit according to any one of claims 16 to 18 wherein each individual active agent is present in an amount from 2mg to 500mg.

20. A combination therapy dose unit according to any one of claims 16 to 19, comprising 100 mg bismuth, 200 mg tetracyclin and 200 mg metronidazole.

21. A combination therapy dose unit according to anyone of claims 16 to 20, comprising a proton pump inhibitor in the amount of between 2mg and 40mg.

22. A combination therapy dose unit according to any one of claims 16 to 21, further comprising EDTA and/or vitamin E.

23. A combination therapy dose unit according to any one of claims 16 to 22, in the form of a tablet.

24. A combination therapy dose unit according to any one of claims 16 to 23 wherein the dose units are individually packaged in blister packs.

25. A method of preventing or treating a disorder in a host requiring administration of a plurality of active agents, comprising the administration of a combination therapy dose unit according to any one of claims 16 to 24.

26. A method according to claim 25, further comprising co-administration of separate dose units comprising other active agents.

27. A method according to claim 25 or claim 26, wherein the disorder is a gastrointestinal disorder.

28. A method according to any one of claims 25 to 27, wherein the disorder is due to or associated with an infection with *Helicobacter.pylori*.

29. A method of preventing interaction between two active agents, substantially as hereinbefore described with reference to any one of the Examples.

30. A combination therapy dose unit, substantially as hereinbefore described with reference to any one of the Examples.

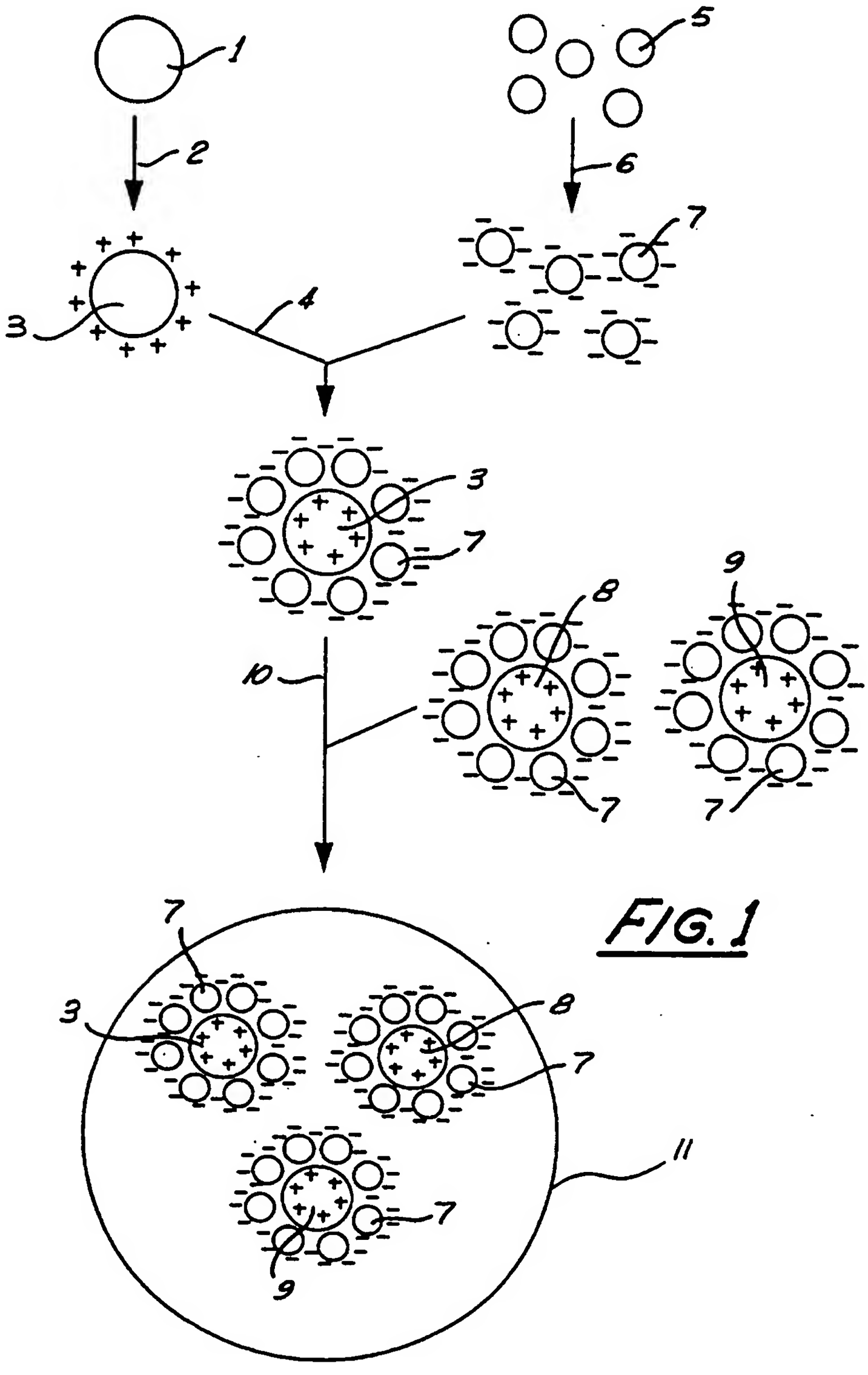

FIG. 1

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 95/00434

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]: A61K 9/20, 9/16, 31/29, 31/65, 31/415, 31/43, 31/71, 31/44, Bo1J 13/10, A61J 3/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC : A61K, A61J 3/00, B01J 13/10

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU : IPC as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPAT, JAPIO, CASM, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	AU,B, 25405/88 (623868) (BORODY) 2 May 1989 pages 3-6	
A	AU,A, 24584/92 (GLAXO GROUP LIMITED) 25 March 1993 pages 3-4	
A	AU,A, 12472/92 (THE PROCTER & GAMBLE COMPANY) 17 August 1992 entire document	

[X] Further documents are listed in the continuation of Box C [ ] See patent family annex

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Date of the actual completion of the international search	Date of mailing of the international search report
25 September 1995	24 OCTOBER 1995
Name and mailing address of the ISA/AU AUSTRALIAN INDUSTRIAL PROPERTY ORGANISATION PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No.: (06) 285 3929	Authorized officer TAMARA NIZNIK Telephone No.: (06) 283 2260

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INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 95/00434

C (Continuation) **DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	AU,B, 65467/69 (449567) (BAYER AKTIENGESELLSCHAFT) 24 June 1971 entire document	
A	GB,A, 2128350 (CANON KABUSHIKI KAISHA) 26 April 1984 page 6, line 6-10	
A	GB,A, 2061983 (SINLOIHI COMPANY LIMITED) 20 May 1981 page 1, line 5-8	
A	GB,A, 2029425 (SINLOIHI COMPANY LIMITED) 19 March 1980 page 1, line 35-43	

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.
PCT/AU 95/00434

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
AU	25405/88	CA	1330759	DE	3887353	EP	439453
		JP	3503404	US	5196205		
AU	24584/92	CA	2078579	EP	533281	FR	2682040
		GB	2259647	JP	6092850		
AU	12472/92	US	5192752	WO	9211848		
GB	2128350	DE	3332621	GB	2128350	JP	59048771
		US	4565764				
GB	2061983	CA	1142812	DE	3039568	FR	2467857
		GB	2061983	JP	56059802		
GB	2029425	CA	1124916	DE	2927249	FR	2430427
		GB	2029425	JP	55009632	US	4314932

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